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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,753	08/08/2006	Jonathan Cebon	029860-0145	3988

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,753	CEBON ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/10/06, 3/19/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/19/09,1/28/08,3/29/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 8/10/06 and 3/19/09 are acknowledged and have been entered.

2. Applicant's election of Group III (claims 20-27) and species of ISCOMATRIX as the saponin-based adjuvant comprising a sterol in Applicant's amendment filed 3/19/09 is acknowledged.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP. 818.03(a)).

Claims 20-27 read on the elected species and are presently being examined.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 20-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating a subject suffering from a cancer, the cells of which express NY-ESO-1, comprising administering to said subject an amount of a composition containing full length NY-ESO-1 protein and ISCOM adjuvant or ISCOMATRIX adjuvant, does not reasonably provide enablement for a method for treating a subject suffering from a cancer, the cells of which express NY-ESO-1, comprising administering to said subject an amount of a composition containing other fragment(s) or variants thereof of NY-ESO-1 protein, or homologues or polytopes of NY-ESO-1, with a saponin based adjuvant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant has broadly claimed a method of treating a subject suffering from a cancer, the cells of which express NY-ESO-1, comprising administering to said subject an amount of a composition containing NY-ESO-1 protein and a saponin based adjuvant, sufficient to induce an antibody response, or in addition, both a $CD4^+$ and a $CD8^+$ T cell response, including wherein the saponin may be an ISCOM or an ISCOMATRIX adjuvant, and including the limitations recited in the other dependent claims.

However, the specification discloses that "any fragment of NY-ESO-1 is considered a part of the definition of proteins used herein. Fragment refers to any portion of the full-length NY-ESO-1 molecule which is large enough to be processed intracellularly, into a peptide which then forms a complex with an MHC molecule, be it MHC class I or class II..." The specification further discloses that synthetic polytopes containing a plurality of

amino acid sequences found in NY-ESO-1 that when concatenated to each other in such a way that they can be processed intracellularly to MHC binding peptides are also included in the definition of NY-ESO-1 protein [0093]. Also part of the definition are SEQ ID NO: 8 of US Patent No. 6,525,177 [0093] as well as homologues of molecules which correspond to amino acid sequences found in SEQ ID NO: 8", homology being used herein refers to molecules that are at least 70%-90% identical "to all or part of the amino acid sequence of NY-ESO-1 referred to herein, as long as they contain at least one amino acid sequence which corresponds to an MHC Class I or MHC Class II binder" [0094]. The specification also discloses "Also part of the invention is the homologous protein antigen LAGE...which contains many immunogenic peptides shared with NY-ESO-1...Also part of the invention are combinations of NY-ESO-1 or LAGE..." [0095]. The specification at [0096] discloses that novel antigenic peptides of NY-ESO described herein are also part of the invention. Such peptides can be found, for example, at [0043], and are peptides that when loaded onto PBMCs, can stimulate either $CD8^+$ T cells or $CD4^+$ T cells *in vitro*. However, even though these peptides were recognized by T cells from a vaccinated (with the full length protein/ISCOM composition) patient, and some were recognized as well by T cells from six other vaccinated patients, it is unpredictable if these antigenic peptides are immunogenic, and if immunogenic, can by themselves or in combination produce a clinical response in "treating a subject."

Evidentiary reference Bergman *et al* (J Virol. 1994, 68(8): 5306-5310) teach a discrepancy between antigenicity and immunogenicity, *i.e.,* failure to induce CTL despite highly efficient recognition *in vitro* (see entire reference).

It is also unpredictable in the case of fragments, polytopes, or homologs that are at least 70%-90% identical to all or part of the amino acid sequence of NY-ESO-1 and comprise at least one amino acid sequence which corresponds to a peptide that binds one of the hundreds of MHC class I or class II molecules, if these are immunogenic and produce a clinical response in "treating a subject."

Evidentiary reference Celis *et al* (Molecular Immunol. 3: 1423-1430, 1994) teach that although algorithms exist to predict MHC binding, in order to establish whether a peptide is immunogenic said peptide needs to be tested in assays that actually establish that a peptide is immunogenic. Celis *et al* further teach that "In addition to MHC binding, other factors such as antigen processing, peptide transport and the composition of the T-cell receptor repertoire could determine whether any of these peptides can function as effective CTL antigens (see entire reference).

Evidentiary reference Ochoa-Garay *et al* (Molecular Immunol. 34: 273-281, 1994) teach that "In summary, the results in this report indicate that the immunogenicity of a peptide cannot always be predicted from its affinity for class I or the presence of class I binding motifs. In addition, our data show that variables such as CTL precursor frequency, peptide hydrophobicity and stability can influence the in vitro induction of CTL responses" (especially page 279, last sentence and continuing onto page 280). Evidentiary reference Karin *et al* (J. Exp. Med. 180: 2227-2237, 1994) teach that a single substitution in an amino acid, wherein said amino acid plays no role in MHC binding can completely abrogate the immunogenicity of an otherwise immunogenic peptide (especially Summary and Table 1).

Evidentiary references Van der Most *et al* (J. Immunol. 1996, 157: 5543-5554 and Virology 1998, 240: 158-167) teach that although an antigenic protein may contain multiple motif-fitting peptides, CTL responses are usually directed against a very limited number of immunodominant epitopes and that immunodominance appears to be determined by a variety of factors including binding affinity to HLA (and motif binding peptides bind with a wide range of affinities due to secondary anchor residues and secondary effects), intracellular processing of peptides determines whether at which level a particular peptide will be presented at the cell surface, and holes in the T cell repertoire restrict CTL responses. Van der Most *et al* also teach that a peptide from NP with the second highest binding affinity (IC50= 4.8nM) after the immunodominant peptide for L^d, is not recognized by LCMV-restricted CTLs.

Evidentiary reference Chang *et al* (J. Immunol. 1999, 162: 1156-1164) teach a peptide that was immunogenic in only a single patient despite similar HLA-binding affinity.

The instant specification discloses that "in essence, an ISCOM vaccine describes a vaccine comprising saponin, sterol and antigen wherein the antigen is associated with the saponin:sterol complex via hydrophobic interaction. An ISCOMATRIX vaccine comprises the same components but the antigen is not associated by hybrophobic interactions." (See page 3 at [0007]).

The specification discloses that the combination of NY-ESO-1 protein and ISCOM was effective in inducing a combined cellular and humoral response to NY-ESO-1, and both known and previously unknown T cell responses were identified, in the context of both MHC class I and Class II responses, more than did the use of protein alone [0090]. In terms of treatment, the specification discloses that the combination of NY-ESO-1 protein and ISCOM *vs* protein alone showed a significant difference in time to relapse [0049].

Evidentiary reference Maraskovsky *et al* (Clin. Canc. Res. 10: 2879-2890, 2004) teach that administration of the full length NY-ESO-1 protein formulated with ISCOMATRIX adjuvant induce both $CD8^+$ and $CD4^+$ T cells (especially abstract).

Thus, the evidentiary reference establish unpredictability in the art of cancer immunotherapy with regard to the issues presented herein.

It is therefore unpredictable, and the instant specification does not provide sufficient guidance, as to which fragments or variants thereof, or homologs, or polytopes of NY-ESO-1 when formulated with a saponin based adjuvant, including an ISCOM or an ISCOMATRIX adjuvant, are sufficient to "treat" a subject suffering from an NY-ESO-1 positive cancer, wherein an antibody response to NY-ESO-1 is induced, or including wherein both a $CD8^+$ and $CD4^+$ T cell response are induced.

Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 contains the trademark or trade names "ISCOM" and "ISCOMATRIX". Where a trademark or trade name is used in a claims as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 USC 112, second paragraph, See Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark or the trade names "ISCOM" and "ISCOMATRIX" are used to identify or describe saponin based adjuvants and accordingly, the identification or the description is indefinite. The relationship between a trademark or trade name and the product it identifies may be uncertain and arbitrary. The formula or characteristics of the product may change from time to time and yet it may continue to be sold under the same trademark or trade name.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 20-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Cebon *et al* (Proc. Amer. Soc. Clin. Oncol. 21: 6/2002, abstract 86 (of record) and presentation slides).

Cebon *et al* teach administering a composition comprising full length NY-ESO-1 protein and ISCOM adjuvant intramuscularly to patients with NY-ESO-1 positive tumors in order to evaluate the safety and immunogenicity of the composition and to correlate clinical response, wherein the amount of NY-ESO-1 protein ranges from 10 ug to 100 ug. Cebon *et al* teach that ISCOMs are saponin-based adjuvants known to stimulate antibody responses and induce T helper cell as well as cytotoxic T lymphocyte responses in a variety of animal models and human clinical trials.

Although Cebon *et al* do not explicitly teach the amount of ISCOM administered, Cebon *et al* teach that the control amount of ISCOM administered was 100 ug. Therefore, it appears that the amount of ISCOM in the composition with NY-ESO-1 at least for the 100 ug NY-ESO-1 administration is equal in amount. Although Cebon *et al* do not correlate the clinical response in their study, immunization resulted in both humoral and cellular responses. In addition, the protocol used by Cebon *et al* is the same as that disclosed in the instant specification. Therefore, the claimed process appears to be the same as the process of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the process of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the process of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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May 19, 2009

/G.R. Ewoldt/
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